REMARKS

Claims 1-6, 21-35, and 51-73 are pending in the application.

I. Interview Summary

Applicant wishes to thank the Examiner for the courtesy extended to Applicant's representative in the interview held on April 27, 2004 ("the Interview") to address the issues outstanding in the instant application.[1] Specifically, the rejection of Claims 21-35 and 51-73 under 35 U.S.C. § 251 based on new matter, and the rejection of Claims 21-25, 31-35, and 51-68 under 35 U.S.C. § 112, first paragraph, for alleged lack of written description were discussed. Further, the filing of a supplemental oath under 37 CFR § 1.175(b)(1) was discussed, and Applicant's representative agreed to file such supplemental oath once the claims are otherwise in condition for allowance, as provided by MPEP § 1444.

With regard to the new matter rejection under Section 251, two issues were addressed, -- (1) support for the term *3'-polynucleotide*, and (2) support for 3'- and 5'-flap length ranges of 1-10 and 1-20 nucleotide, respectively. The first issue was resolved as Applicant's representative pointed to support in the disclosure of the instant reissue application for the term *3'-polynucleotide*. As to the second issue, Applicant's representative agreed to consider amending the claims to include lengths described *ipsis verbis* in the disclosure of the instant reissue application.

1 It is noted that the interview was originally scheduled for January 29, 2004, *see* Applicant Initiated Interview Request form filed on January 26, 2004, but had to be rescheduled for April 27, 2004.

As to the written description rejection under Section 112, first paragraph, Applicant's representative pointed out that under the current legal standard, eight species provide sufficient written description for a genus of compounds used in a claimed method. Further, Applicant's representative agreed to consider an amendment defining the strand of the 5',3'-double flap structure cleaved by a FEN-1 to more specifically characterize the nature of the substrate. Specifically, Applicant's representative agreed to consider an amendment specifying that the 5'-polynucleotide of the double flap structure is the one cleaved by a FEN-1.

The details of the various issues addressed during the interview are discussed in Applicant's response to the outstanding Office Action hereinbelow.

II. The Amendments

The Claims have been amended, without prejudice, for the purpose of expediting prosecution of the present application. The amendments do not introduce new matter and they are fully supported by the disclosure of the instant reissue application as originally filed. Entry of the amended claims pursuant to 37 C.F.R. §1.111 is requested.

Specifically, Claim 21 has been amended to recite the step of "cleaving the 5'-probe of the 5',3'-double flap structure with a FEN-1 polypeptide." Support for this amendment can be found in Figure 5 and its description on page 4506 of Harrington & Lieber, 1995, *J. Biol. Chem.* 270:4503-4508 ("Harrington & Lieber"), incorporated by reference into the disclosure of the present reissue application. Claims 31, 33, 56, 58, 62, and 64 have been amended, and new Claims 74-76 have been added, to recite certain embodiments that are described *ipsis verbis* in

the disclosure of the present reissue application. Support for these amendments can be found in the disclosure at, for example, Col. 46:46-48 and in Figure 5 and page 4606 of the incorporated Harrington & Lieber article.

A marked-up copy of the claims showing the present amendments as compared to the claims as pending prior to entry of the instant amendment is attached hereto as *Appendix A*.

III. Formalities

The reissue oath/declaration is objected to under 37 CFR § 1.175(b)(1). Applicant wishes to thank the Examiner for supplying language for a supplemental oath that would overcome the objection. Pursuant to MPEP § 1444, and as discussed in the Interview, Applicant will submit such a supplemental oath once the claims are allowable.

Applicant will also surrender the original patent document once the claims are allowable.

IV. The Rejections

A. The Rejection Of Claims 21-35 And 51-73 Under 35 U.S.C. § 251

Claims 21-35 and 51-73 stand rejected under 35 U.S.C.§ 251 as allegedly being based upon new matter added to the patent for which reissue is sought. First, with regard to all rejected claims, the Office Action alleges that while the disclosure provides support for a "5'-polynucleotide probe," it does not mention a "*3'-polynucleotide probe.*" Second, with regard to Claims 31, 33, 56, 58, 62, and 64, the Office Action additionally states that there is no support for the recited nucleotide ranges of 1-10 and 1-20, respectively. The rejections are traversed.

1. The Disclosure Supports Methods, Complexes And Kits Utilizing 3'-Polynucleotide Probes

Applicant submits that the recited "3'-polynucleotide probe" is clearly defined and described in the disclosure of the instant reissue application. Specifically, the disclosure states:

> Typically, the probe polynucleotide comprises two portions, a first portion which hybridizes to the target sequence and a second portion which is adjacent to said first portion and which forms a flap strand; frequently *an adjacent polynucleotide is present which hybridizes to the portion of the target polynucleotide immediately 5' to the portion of the target polynucleotide which hybridizes to the probe polynucleotide sequence.*

See specification at col. 11:17-24. (Emphasis added).

As explained during the Interview, the *adjacent polynucleotide* is the 3'-polynucleotide probe recited in the claims. An embodiment of an adjacent, or 3'-, polynucleotide probe including an unhybridized "flap" region as presently claimed is illustrated in Figure 5 of the incorporated Harrington & Lieber article. As disclosed in this article, such 3'-polynucleotide probes can serve as an adjacent strand (F_{adj} strand) to permit efficient cleavages of the 5'-flap strand of the resultant 3', 5'-double flap structure by a FEN-1:

> When Double Flaps 1 and 2 were tested in this cleavage assay, we found that the 1- and 10-nucleotide 3'-flap strands served as an $F_{adj.}$ strand, allowing FEN-1 to cleave the 5'-flap strand efficiently (Fig. 5B). Furthermore, cleavage of the double flap structures by FEN-1 was more efficient than that of the standard 5'-flap structure.

See Harrington & Lieber at page 4506.

Thus, as agreed in the Interview, the disclosure of the instant reissue application provides adequate written description support for a 3'-polynucleotide probe as recited in Claims 21-35 and

51-73. Accordingly, it is requested that this basis for the rejection of these claims under 35 U.S.C. § 251 be removed.

2. The Disclosure Provides Support For Various Flap Lengths And Length Ranges

The Office Action contends that neither the specification of the issued patent nor the incorporated Harrington & Lieber article provide adequate support for the flap length ranges recited in Claims 32, 24, 56, 58, 62, and 64. Although Applicant disagrees with the Office Action's characterization of the instant disclosure and the propriety of the rejection for reasons of record, in order to expedite prosecution, Applicant has amended these claims, without prejudice, and added new Claims 74-76 to recite certain embodiments that are described *ipsis verbis* in the disclosure.

In particular, Claims 31, 56 and 62 have been amended to recite a 3'-polynucleotide having a 3'-flap length of 10 nucleotides, and Claims 32, 57 and 63 have been amended to recite a 3'-flap length of 1 nucleotide. Support for these amendments is found in Figures 5 and page 4506 of the incorporated Harrington & Lieber article, which describes 5',3'-double flap structures in which the 3'-probe has a flap of 1 nucleotide (*see* double flap No.1 in Figure 5 at page 4506) or 10 nucleotides (*see* double flap No. 2 in Figure 5 at page 4506) in length. Both of these double flap structures are cleaved by a FEN-1.

Claims 33, 58, and 64 have been amended, and new Claims 74-76 have been added, to recite a 5'-polynucleotide having a 5'-flap length of 1-5, and 20 nucleotides, respectively. Support for these amendments is found, for example, at Col. 46:46-58 and the incorporated

Harrington & Lieber article at page 4506, Figure 5 (e.g., double flaps Nos. 1 and 2), where 5'-polynucleotide probes having 5'-flaps varying from 1-5 nucleotides, and of 20 nucleotides, in length, are specifically described. In addition, it is specifically taught that cleavage of the 5'-flap is independent of its length (*see* Col. 19:21-22).

Accordingly, the amended and added claims are fully supported by the original disclosure of the instant reissue application.

3. The Recited 5',3'-Double Flap Structures Are Cleaved By FEN-1 Polypeptides

The Office Action also states that the issued patent teaches that a 3'-flap structure was not cleaved by a FEN-1 polypeptide (*see* Col. 46:65-67), and concludes from this teaching that 3'-flap structures are unsuitable for use in the presently claimed methods.

Applicant concurs that the teaching at Col. 46:65-67 indicates 3'-flaps are not cleaved by FEN-1 polypeptides. However, the instant claims do not recite 3'-flap structures. They recite 5', 3'-double flap structures. Binding and cleavage of such double-flap structures by FEN-1 polypeptides is taught in the instant disclosure at, for example, in Figure 5 of the incorporated Harrington & Lieber article, and its associated text (*see* Harrington & Lieber at page 4605). Thus, the recited structures are clearly suitable for use in the claimed methods.

4. All Claims Of The Instant Reissue Application Satisfy 35 U.S.C. § 251

Claims presented in a reissue application do not constitute new matter under 35 U.S.C. § 251 when the claims are supported by the original disclosure in the manner prescribed by the first paragraph of 35 U.S.C. § 112. Thus, in view of the above, Claims 21-35, 51-73, and new Claims

74-76 do not introduce new matter into the instant reissue application. Accordingly, Applicant respectfully requests that the rejection of Claims 21-35 and 51-73 under 35 U.S.C. § 251 be withdrawn.

B. The Rejection Of Claims 21-25, 31-35, And 51-68 Under 35 U.S.C. § 112, First Paragraph

Claims 21-25, 31-35, and 51-68 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description. The Office Action states three bases for the rejection. First, it alleges that the claims do not define the structure of the recited FEN-1 endonuclease. Second, it alleges that the claims do not define the structure of the substrate cleaved by FEN-1. Third, the Office Action alleges that flap length ranges of 1-10 and 1-20 nucleotides, respectively, are not described. The rejection is traversed.

1. The Structure Of The Endonuclease Used In The Claimed Method Is Readily Described By Virtue Of Description Of Eight Representative Species

In accordance with the guidance provided by the Written Description Guidelines (Federal Register 66(4):1092-1111 (January 5, 2001) at page 1106) and *The Regents* decision,[2] Applicant has pointed out eight exemplary species of FEN-1 polypeptides that are specifically described in the original disclosure, *i.e.*, the human FEN-1 of SEQ ID NO:1, the mouse FEN-1 of SEQ ID NO:3, the yeast FEN-1 of SEQ ID NO:5, the Δrad2 of SEQ ID NO:7 and the various FEN-1 enzymes found in extracts from calf thymus, rabbit reticulocytes, Chinese hamster fibroblasts and Drosophila embryos (for these latter FEN-1 species *see* Col. 44:23-27). As discussed during the

2 *Regents of the Univ. of Cal. v. Eli Lilly & Co., Inc.*, 43 USPQ2d 1398 (Fed. Cir. 1997).

Interview, eight exemplary species re sufficiently representative of a genus so as to provide adequate written description support for the genus, in particular given the fact that the rejected claims are directed to methods of use and kits, and not to the FEN-1 polypeptide molecules *per se*.

Specifically, as discussed during the Interview, the rejected claims are directed to a method of detecting the presence of a target nucleic acid sequence in a sample using a FEN-1 polypeptide and polynucleotide probes capable of being cleaved by a FEN-1 polypeptide (*see* Claims 21-25, and 31-35), a hybridization complex including polynucleotide probes capable of being cleaved by a FEN-1 polypeptide (*see* Claims 51-58), and a kit for detecting the presence of a target nucleic acid in a sample including polynucleotide probes capable of being cleaved by a FEN-1 polypeptide (*see* Claims 59-68). None of these claims is directed to a FEN-1 polypeptide *per se*.

As agreed during the Interview, applying the legal standard, and in particular in light of the recent *Rochester* decision,[3] a description of *eight* species in the context of claims reciting a method, a hybridization complex, and a kit for performing the method, constitutes adequate written description support for the recitation of a genus.

Thus, this basis for the written description rejection should be removed.

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3 *University of Rochester v. G.D. Searle & Co., Inc., Monsanto Company, Pharmacia Corporation, and Pfizer, Inc.*, 69 USPQ2d 1886 (Fed. Cir. 2004).

2. The Structure Of The Strand That is Cleaved by a FEN-1 Is Readily Defined In The Claims As Amended

The method claims also stand rejected because the structure of the strand of the 5',3'-double flap structure that a FEN-1 polypeptide uses as substrate is allegedly not readily defined.

While Applicant does not agree that this is a proper basis for a written description rejection, in order to expedite prosecution, the claims have been amended to specifically define the strand of the 5',3'-double flap structure cleaved by the FEN-1 polypeptide. Specifically, Claim 21 has been amended to recite the step of "cleaving *the 5'-probe* of the 5',3'-double flap structure with a FEN-1 polypeptide." *See* Claim 21, step (b). Accordingly, this basis for lack of description should also be removed.

3. The Specification Provides Written Description For Various Flap Lengths And Length Ranges

The Office Action contends that the recited flap length ranges of 1-10 and 1-20 nucleotides, respectively, as recited in Claims 32, 24, 56, 58, 62, and 64, are not described. Section IV.A.2., *supra*.

4. All Claims Satisfy The Written Description Requirement Of 35 U.S.C. § 112, First Paragraph

In view of the above, Claims 21-25, 31-35, and 51-68 satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. All of the method steps of Claims 21-25 and 31-35, as well as the structure of FEN-1 polypeptides and the 5',3'-double flap substrates necessary for carrying out the claimed method are described. Likewise, the hybridization

complex of Claims 51-58, and the probes and FEN-1 polypeptides comprising the kits of Claims 59-68 are described. The original disclosure therefore reasonably apprises one skilled in the art that Applicant was, at the time the original application was filed, in possession of the claimed inventions. This is all the written description requirement of Section 112, first paragraph demands. Accordingly, Applicant requests that the rejection of Claims 21-25, 31-35, and 51-68 for lack of written description be withdrawn.

CONCLUSION

In view of the above remarks, pending Claims 1-6, 21-35, and 51-73 are believed to satisfy all the criteria for patentability and are believed to be in condition for allowance. Early notification to this effect is earnestly solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (415) 781-1989. The commissioner is authorized to charge any underpayment or credit any overpayment to Deposit Account No. 50-2319 (order no. 470438-00007) for any matter in connection with this response, including any fee for extension of time, which may be required.

Respectfully submitted,

DORSEY & WHITNEY LLP

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By: _____
Birgit Millauer
Registration No. 43,341

Customer No. 32940
Dorsey & Whitney, LLP
Intellectual Property Department
Four Embarcadero Center, Suite 3400
San Francisco, California 94111-4187
Tel: (415) 781-1989
Fax: (415) 398-3249

APPENDIX A

1. (Previously presented) An isolated polynucleotide encoding a FEN-1 polypeptide as shown in SEQ ID NO:1 or SEQ ID NO:3, or a fragment of said polypeptide having flap endonucleolytic cleavage activity.

2. (Previously presented) An isolated polynucleotide, wherein said polynucleotide comprises a nucleotide sequence selected from the group consisting of SEQ ID NOS:29-51.

3. (Previously presented) An isolated polynucleotide of Claim 2, wherein said polynucleotide comprises the sequence of SEQ ID NO:28.

4. (Previously presented) A host cell comprising the polynucleotide of Claim 1.

5. (Previously presented) A non-mammalian host cell comprising a mammalian FEN-1 polypeptide of Claim 1.

6. (Previously presented) The polynucleotide of Claim 1 that is full length.

21. (Currently amended) A method of detecting the presence of a predetermined target nucleic acid sequence in a sample, comprising the steps of:

(a) contacting, under conditions in which a FEN-1 polypeptide exhibits cleavage activity, a sample suspected of containing a target nucleic acid comprising the predetermined target sequence with:

(i) a 5'-polynucleotide probe capable of being cleaved by a FEN-1 polypeptide, comprising a 3'-region that is capable of specifically hybridizing under said cleavage conditions to a first portion of the target sequence and a 5'-region located immediately 5' to the 3'-region; and

(ii) a 3'-polynucleotide probe comprising a 5'-region that is capable of specifically hybridizing under said cleavage conditions to a second portion of the target sequence which is located immediately 3' to the first portion and a 3'-region located immediately 3' to the 5'-region,

such that the 3'-region of the 5'-probe and the 5'-region of the 3'-probe specifically hybridize immediately contiguously with one another to the first and second portions, respectively, of the target sequence to form a 5',3'-double flap structure cleavable by a FEN-1 polypeptide;

(b) cleaving the 5'-probe of the 5',3'-double flap structure with a FEN-1 polypeptide; and

(c) detecting the presence or absence of, and/or quantifying the amount of, FEN-1 polypeptide-generated cleavage, thereby detecting the presence of the target sequence in the sample.

22. (Previously amended) The method of Claim 21 in which the 5'-probe contains a detectable label.

23. (Previously amended) The method of Claim 22 in which the 5'-region of the 5'-probe contains the detectable label.

24. (Previously amended) The method of Claim 23 in which the 5'-end of the 5'-probe contains the detectable label.

25. (Previously amended) The method of Claim 21 in which the 5'-probe is immobilized on a support.

26. (Previously amended) The method of Claim 21 in which the FEN-1 polypeptide is encoded by a polynucleotide comprising a sequence selected from the group of sequences consisting of SEQ ID NOS: 29-51.

27. (Previously amended) The method of Claim 26 in which the FEN-1 polypeptide is encoded by a polynucleotide comprising SEQ ID NO:28.

28. (Previously amended) The method of Claim 21 in which the FEN-1 polypeptide comprises the amino acid sequence shown in SEQ ID NO:1 or a fragment thereof having 5'-flap endonucleolytic cleavage activity.

29. (Previously amended) The method of Claim 21 in which the FEN-1 polypeptide comprises the amino acid sequence shown in SEQ ID NO:3 or a fragment thereof having 5'-flap endonucleolytic cleavage activity.

30. (Previously amended) The method of Claim 21 in which the FEN-1 polypeptide comprises the amino acid sequence shown in SEQ ID NO:5 or SEQ ID NO:7 or a fragment thereof having 5'-flap endonucleolytic cleavage activity.

31. (Currently amended) The method of Claim 21 in which the 3'-region of the 3'-probe is [1 to] 10 nucleotides in length.

32. (Previously amended) The method of Claim 21 in which the 3'-region of the 3'-probe is 1 nucleotide in length.

33. (Currently amended) The method of Claim 21 in which the 5'-region of the 5'-probe is 1 to [20] 5 nucleotides in length.

34. (Previously amended) The method of any one of Claims 21-33 in which the amount of FEN-1 polypeptide-generated cleavage is quantified.

35. (Previously amended) The method of any one of Claims 21-33 in which the presence or absence of FEN-1 polypeptide-generated cleavage is detected.

51. (Previously amended) A hybridization complex comprising:

(a) a bridge polynucleotide comprising a first portion and second portion located immediately 3' to the first portion;

(b) a first polynucleotide probe capable of being cleaved by a FEN-1 polypeptide, comprising a 3'-region and a 5'-region located immediately 5' to the 3'-region; and

(c) a second polynucleotide probe comprising a 5'-region and a 3'-region located immediately 3' to the 5'-region,

wherein the 3'-region of the first probe and the 5'-region of the second probe are specifically hybridized immediately contiguously with one another to the first and second portions, respectively, of the same bridge polynucleotide molecule, thereby forming a hybridization complex.

52. (Previously amended) The hybridization complex of Claim 51 in which the first probe contains a detectable label.

53. (Previously amended) The hybridization complex of Claim 52 in which the 5'-region of the first probe contains the detectable label.

54. (Previously amended) The hybridization complex of Claim 53 in which the 5'-end of the first probe contains the detectable label.

55. (Previously amended) The hybridization complex of Claim 51 in which the first probe is immobilized on a substrate.

56. (Currently amended) The hybridization complex of Claim 51 in which the 3'-region of the second probe is [1 to] 10 nucleotides in length.

57. (Previously amended) The hybridization complex of Claim 56 in which the 3'-region of the second probe is 1 nucleotide in length.

58. (Currently amended) The hybridization complex of Claim 51 in which the 5'-region of the first probe is 1 to [20] 5 nucleotides in length.

59. (Previously amended) A kit for use in detecting the presence of a predetermined target nucleic acid sequence in a sample, comprising:

(a) a FEN-1 polypeptide;

(b) a first polynucleotide probe capable of being cleaved by a FEN-1 polypeptide, comprising a 3'-region capable of specifically hybridizing under FEN-1 polypeptide cleavage conditions to a first portion of ~~a~~ the predetermined target sequence and a 5'-region located immediately 5' to the 3'-region; and

(c) a second polynucleotide probe comprising a 5'-region capable of specifically hybridizing under FEN-1 polypeptide cleavage conditions to a second portion of the target sequence which is located immediately 3' to the first portion and a 3'-region located immediately 3' to the 5'-region,

wherein the 3'-region of the first probe and the 5'-region of the second probe are capable of specifically hybridizing immediately contiguously with one another to the first and second portions, respectively, of the target sequence to form a 5',3'-double flap structure that is capable of being cleaved by the FEN-1 polypeptide.

60. (Previously amended) The kit of Claim 59 further in which the first or second probe contains a detectable label.

61. (Previously amended) The kit of Claim 59 in which the FEN-1 polypeptide contains a detectable label.

62. (Currently amended) The kit of Claim 59 in which the 3'-region of the second probe is [1 to] 10 nucleotides in length.

63. (Previously amended) The kit of Claim 59 in which the 3'-region of the second probe is 1 nucleotide in length.

64. (Currently amended) The kit of Claim 59 in which the 5'-region of the first probe is 1 to [20] 5 nucleotides in length.

65. (Previously amended) The kit of Claim 59 in which the first probe contains a detectable label.

66. (Previously amended) The kit of Claim 65 in which the 5'-region of the first probe contains ~~a~~ the detectable label.

67. (Previously amended) The kit of Claim 66 in which the 5'-end of the first probe contains the detectable label.

68. (Previously amended) The kit of Claim 59 in which the first or second probe is immobilized on a substrate.

69. (Previously amended) The kit of any one of Claim 59-68 in which the FEN-1 polypeptide is encoded by a polynucleotide comprising a sequence selected from the group of sequences consisting of SEQ ID NOS: 29-51.

70. (Previously amended) The kit of any one of Claims 59-68 in which the FEN-1 polypeptide is encoded by a polynucleotide comprising SEQ ID NO. 28.

71. (Previously amended) The kit of any one of Claims 59-68 in which the FEN-1 polypeptide comprises the amino acid sequence shown in SEQ ID NO:1 or a fragment thereof having 5'-flap endonucleolytic cleavage activity.

72. (Previously amended) The kit of any one of Claims 59-68 in which the FEN-1 polypeptide comprises the amino acid sequence shown in SEQ ID NO:3 or a fragment thereof having 5'-flap endonucleolytic cleavage activity.

73. (Previously amended) The kit of any one of Claims 59-68 in which the FEN-1 polypeptide comprises the amino acid sequence shown in SEQ ID NO:5 or SEQ ID NO:7 or a fragment thereof having 5'-flap endonucleolytic cleavage activity.

74. (New) The method of Claim 21 in which the 5'-region of the 5'-polynucleotide probe is 20 nucleotides in length.

75. (New) The hybridization complex of Claim 51 in which the 5'-region of the first polynucleotide probe is 20 nucleotides in length.

76. (New) The kit of Claim 59 in which the 5'-region of the first polynucleotide probe is 20 nucleotides in length.